General

Guideline Title

VA/DoD clinical practice guideline for the management of chronic obstructive pulmonary disease.

Bibliographic Source(s)

Management of Chronic Obstructive Pulmonary Disease Working Group. VA/DoD clinical practice guideline for the management of chronic obstructive pulmonary disease. Washington (DC): Department of Veterans Affairs, Department of Defense; 2014 Dec. 94 p. [216 references]

Guideline Status

This is the current release of the guideline.

This guideline updates a previous version: Management of COPD Working Group. VA/DoD clinical practice guideline for the management of outpatient chronic obstructive pulmonary disease. Washington (DC): Department of Veterans Affairs, Department of Defense; 2007. 138 p.

This guideline meets NGC's 2013 (revised) inclusion criteria.

Regulatory Alert

FDA Warning/Regulatory Alert

Note from the National Guideline Clearinghouse: This guideline references a drug(s) for which important revised regulatory and/or warning information has been released.

- May 12, 2016 – Fluoroquinolone Antibacterial Drugs : The U.S. Food and Drug Administration (FDA) is advising that the serious side effects associated with fluoroquinolone antibacterial drugs generally outweigh the benefits for patients with sinusitis, bronchitis, and uncomplicated urinary tract infections who have other treatment options. For patients with these conditions, fluoroquinolones should be reserved for those who do not have alternative treatment options.

Recommendations

Major Recommendations

Note from the Department of Veterans Affairs and the Department of Defense (VA/DoD) and the National Guideline Clearinghouse (NGC): The recommendations for the management of chronic obstructive pulmonary disease (COPD) are organized into 4 modules (including diagnosis/assessment and 3 management strategies) with 3 algorithms. The modules with accompanying recommendations are presented below.

See the original guideline document for the algorithm and evidence tables associated with selected recommendations, including level and quality of evidence, strength of recommendation, and supporting evidence citations.

The strength of recommendation grading (Strong For, Weak For, Strong Against, Weak Against) is defined at the end of the "Major Recommendations" field.

Diagnosis and Assessment of COPD

1. The guideline panel recommends that spirometry, demonstrating airflow obstruction (post-bronchodilator forced expiratory volume in one second/forced vital capacity [FEV1/FVC] <70%, with age adjustment for more elderly individuals), be used to confirm all initial diagnoses of COPD. (Strong For)
2. The guideline panel has no recommendations regarding utilization of existing clinical classification systems at this time. (Not Applicable)
3. The guideline panel suggests classification of patients with COPD into two groups:
    a. Patients who experience frequent exacerbations (two or more/year, defined as prescription of corticosteroids, prescription of antibiotics, hospitalization, or emergency department [ED] visit)
    b. Patients without frequent exacerbations

    (Weak For)

4. The guideline panel recommends offering prevention and risk reduction efforts including smoking cessation and vaccination. *Modified from the 2007 Clinical Practice Guideline (CPG) without an updated systematic review of the evidence.* (Strong For)
5. The guideline panel recommends investigating additional comorbid diagnoses particularly in patients who experience frequent exacerbations (two or more/year, defined as prescription of corticosteroids, prescription of antibiotics, hospitalization, or ED visit) using simple tests and decision rules (cardiac ischemia [troponin, electrocardiogram], congestive heart failure [B-type natriuretic peptide (BNP), pro-BNP], pulmonary embolism [D-dimer plus clinical decision rule], and gastroesophageal reflux). (Strong For)
6. The guideline panel suggests that patients with COPD and signs or symptoms of a sleep disorder have a diagnostic sleep evaluation. *Modified from the 2007 CPG without an updated systematic review of the evidence.* (Weak For)
7. The guideline panel suggests that patients presenting with early onset COPD or a family history of early onset COPD be tested for alpha-1 antitrypsin (AAT) deficiency. *Modified from the 2007 CPG without an updated systematic review of the evidence.* (Weak For)
8. The guideline panel recommends that patients with AAT deficiency be referred to a pulmonologist for management of treatment. *Modified from the 2007 CPG without an updated systematic review of the evidence.* (Strong For)

Management of Patients with COPD in the Outpatient Setting

Pharmacologic Therapy

9. The guideline panel recommends prescribing inhaled short-acting beta 2-agonists (SABAs) to patients with confirmed COPD for rescue therapy as needed. *Modified from the 2007 CPG without an updated systematic review of the evidence.* (Strong For)
10. The guideline panel suggests using spacers for patients who have difficulty actuating and coordinating drug delivery with metered-dose inhalers (MDIs). *Modified from the 2007 CPG without an updated systematic review of the evidence.* (Weak For)
11. The guideline panel recommends offering long-acting bronchodilators to patients with confirmed, stable COPD who continue to have respiratory symptoms (e.g., dyspnea, cough). (Strong For)
12. The guideline panel suggests offering the inhaled long-acting antimuscarinic agent (LAMA) tiotropium as first-line maintenance therapy in patients with confirmed, stable COPD who continue to have respiratory symptoms (e.g., dyspnea, cough). (Weak For)
13. The guideline panel recommends inhaled tiotropium as first-line therapy for patients with confirmed, stable COPD who have respiratory symptoms (e.g., dyspnea, cough) and severe airflow obstruction (i.e., post bronchodilator FEV1 <50%) or a history of COPD exacerbations. (Strong For)
14. For clinically stable patients with a confirmed diagnosis of COPD and who have not had exacerbations on short-acting antimuscarinic agents (SAMAs), the guideline panel suggests continuing with this treatment, rather than switching to long-acting bronchodilators. *Modified from the 2007 CPG without an updated systematic review of the evidence.* (Weak For)
15. For patients treated with a SAMA who are started on a LAMA to improve patient outcomes, the guideline panel suggests discontinuing the SAMA. *Modified from the 2007 CPG without an updated systematic review of the evidence.* (Weak For)
16. The guideline panel recommends against offering an inhaled corticosteroid (ICS) in symptomatic patients with confirmed, stable COPD as a first-line monotherapy. (Strong Against)
17. The guideline panel recommends against the use of inhaled long-acting beta 2-agonists (LABAs) without an ICS in patients with COPD who may have concomitant asthma. (Strong Against)
18. In patients with confirmed, stable COPD who are on inhaled LAMAs (tiotropium) or inhaled LABAs alone and have persistent dyspnea on monotherapy, the guideline panel recommends combination therapy with both classes of drugs. (Strong For)

19. In patients with confirmed, stable COPD who are on combination therapy with LAMAs (tiotropium) and LABAs and have persistent dyspnea or COPD exacerbations, the guideline panel suggests adding ICS as a third medication. (Weak For)
20. The guideline panel suggests against offering roflumilast in patients with confirmed, stable COPD in primary care without consultation with a pulmonologist. (Weak Against)
21. The guideline panel suggests against offering chronic macrolides in patients with confirmed, stable COPD in primary care without consultation with a pulmonologist. (Weak Against)
22. The guideline panel suggests against offering theophylline in patients with confirmed, stable COPD in primary care without consultation with a pulmonologist. (Weak Against)
23. There is insufficient evidence to recommend for or against the use of N-acetylcysteine (NAC) preparations available in the US in patients with confirmed, stable COPD who continue to have respiratory symptoms (e.g., dyspnea, cough). (Not Applicable)
24. The guideline panel suggests not withholding cardio-selective beta-blockers in patients with confirmed COPD who have a cardiovascular indication for beta-blockers. (Weak For)
25. The guideline panel suggests using non-pharmacologic therapy as first-line therapy and using caution in prescribing hypnotic drugs for chronic insomnia in primary care for patients with COPD, especially for those with hypercapnea or severe COPD. *Modified from the 2007 CPG without an updated systematic review of the evidence*. (Weak For)
26. For patients with COPD and anxiety, the guideline panel suggests consultation with a psychiatrist and/or a pulmonologist to choose a course of anxiety treatment that reduces, as much as possible, the risk of using sedatives/anxiolytics in this population. *Modified from the 2007 CPG without an updated systematic review of the evidence*. (Weak For)

Oxygen Therapy

27. The guideline panel recommends providing long-term oxygen therapy (LTOT) to patients with chronic stable resting severe hypoxemia (partial pressure of oxygen in arterial blood [PaO_2] <55 mm Hg and/or peripheral capillary oxygen saturation [SaO_2] ≤88%) or chronic stable resting moderate hypoxemia (PaO_2 of 56-59 mm Hg or SaO_2 >88% and ≤90%) with signs of tissue hypoxia (hematocrit >55%, pulmonary hypertension, or cor pulmonale). *Modified from the 2007 CPG without an updated systematic review of the evidence*. (Strong For)
28. The guideline panel recommends that patients discharged home from hospitalization with acute transitional oxygen therapy are evaluated for the need for LTOT within 30-90 days after discharge. LTOT should not be discontinued if patients continue to meet the above criteria. *Modified from the 2007 CPG without an updated systematic review of the evidence*. (Strong For)
29. The guideline panel suggests against routinely offering ambulatory LTOT for patients with chronic stable isolated exercise hypoxemia, in the absence of another clinical indication for supplemental oxygen. (Weak Against)
30. For patients with COPD and hypoxemia and/or borderline hypoxemia (SaO_2 <90%) who are planning to travel by plane, the guideline panel suggests a brief consultation or an e-consult with a pulmonologist. *Modified from the 2007 CPG without an updated systematic review of the evidence*. (Weak For)
31. When other causes of nocturnal hypoxemia have been excluded, the guideline panel suggests against routinely offering LTOT for the treatment of outpatients with stable, confirmed COPD and isolated nocturnal hypoxemia. (Weak Against)

Stable Hypercapnea

32. In the absence of other contributors (e.g., sleep apnea), the guideline panel suggests referral for a pulmonary consultation in patients with stable, confirmed COPD and hypercapnea. (Weak For)

Supported Self-Management

33. The guideline panel suggests supported self-management for selected high risk patients with COPD. (Weak For)
34. The guideline panel suggests against using action plans *alone* in the absence of supported self-management. (Weak Against)

Telehealth

35. The guideline panel suggests using telehealth for ongoing monitoring and support of the care of patients with confirmed COPD. (Weak For)

Pulmonary Rehabilitation

36. The guideline panel recommends offering pulmonary rehabilitation to stable patients with exercise limitation despite pharmacologic treatment and to patients who have recently been hospitalized for an acute exacerbation. (Strong For)

Breathing Exercise

37. The guideline panel suggests offering breathing exercise (e.g., pursed lip breathing, diaphragmatic breathing, or yoga) to patients with dyspnea that limits physical activity. (Weak For)

Nutrition Referral

38. The guideline panel suggests referral to a dietitian for medical nutritional therapy recommendations (such as oral calorie supplementation) to support patients with severe COPD who are malnourished (body mass index [BMI] <20 kg/m^2). (Weak For)

Lung Volume Reduction Surgery (LVRS) and Lung Transplant

39. The guideline panel recommends that any patient considered for surgery for COPD (LVRS and lung transplant) be first referred to a pulmonologist for evaluation. *Modified from the 2007 CPG without an updated systematic review of the evidence*. (Strong For)

Management of Patients in Acute Exacerbation of COPD

40. The guideline panel recommends antibiotic use for patients with COPD exacerbations who have increased dyspnea and increased sputum purulence (change in sputum color) or volume. (Strong For)
41. The guideline panel suggests basing choice of antibiotic on local resistance patterns and patient characteristics.
    a. First-line antibiotic choice may include doxycycline, trimethoprim/sulfamethoxazole (TMP-SMX), second-generation cephalosporin, amoxicillin, amoxicillin/clavulanate, and azithromycin.
    b. Despite the paucity of evidence regarding the choice of antibiotics, the guideline panel suggests reserving broader spectrum antibiotics (e.g., quinolones) for patients with specific indications such as:
        i. Critically ill patients in the intensive care unit (ICU)
        ii. Patients with recent history of resistance, treatment failure, or antibiotic use
        iii. Patients with risk factors for health care associated infections

    (Weak For)

42. For outpatients with acute COPD exacerbation who are treated with antibiotics, the guideline panel recommends a five-day course of the chosen antibiotic. (Strong For)
43. There is insufficient evidence to recommend for or against procalcitonin-guided antibiotic use for patients with acute COPD exacerbations. (Not Applicable)
44. For acute COPD exacerbations, the guideline panel recommends a course of systemic corticosteroids (oral preferred) of 30-40 mg prednisone equivalent daily for 5-7 days. (Strong For)

Management of Patients with COPD in the Hospital or Emergency Department

45. The guideline panel suggests use of airway clearance techniques utilizing positive expiratory pressure (PEP) devices for patients with COPD exacerbations and difficulty expectorating sputum. (Weak For)
46. The guideline panel recommends the early use of non-invasive ventilation (NIV) in patients with acute COPD exacerbations to reduce intubation, mortality, and length of hospital stay. (Strong For)
47. The guideline panel recommends the use of NIV to support weaning from invasive mechanical ventilation and earlier extubation of intubated patients with COPD. (Strong For)

Definitions:

Quality of Evidence and Definitions*

High quality — Further research is very unlikely to change confidence in the estimate of effect.
Moderate quality — Further research is likely to have an important impact on confidence in the estimate of effect and may change the estimate.
Low quality — Further research is very likely to have an important impact on confidence in the estimate of effect and is likely to change the estimate.
Very low quality — Any estimate of effect is very uncertain.

*Guyatt, G. H., Oxman, A. D., Vist, G. E., Kunz, R., Falck-Ytter, Y., Alonso-Coello, P., Schünemann, H. J. & the GRADE Working Group. (2008). GRADE; An emerging consensus on rating quality of evidence and strength of recommendations. *BMJ, 336*, 924-926.

Strength of Recommendations

The relative strength of the recommendation is based on a binary scale, "Strong" or "Weak." A strong recommendation indicates that the Work Group is highly confident that desirable outcomes outweigh undesirable outcomes. If the Work Group is less confident of the balance between desirable and undesirable outcomes, they present a weak recommendation.

Similarly, a recommendation for a therapy or preventive measure indicates that the desirable consequences outweigh the undesirable consequences. A recommendation against a therapy or preventive measure indicates that the undesirable consequences outweigh the desirable consequences.

The grade of each recommendation is presented as part of a continuum:

- Strong For (or "The guideline panel recommends offering this option …")
- Weak For (or "The guideline panel suggests offering this option …")
- Weak Against (or "The guideline panel suggests not offering this option …")
- Strong Against (or "The guideline panel recommends against offering this option …")

Note that weak (For or Against) recommendations may also be termed "Conditional," "Discretionary," or "Qualified." Recommendations may be conditional based upon patient values and preferences, the resources available, or the setting in which the intervention will be implemented. Recommendations may be at the discretion of the patient and clinician or they may be qualified with an explanation about the issues that would lead decisions to vary.

Clinical Algorithm(s)

The following algorithms are provided in the original guideline document:

- Algorithm A: Management of COPD in Primary Care
- Algorithm B: Management of Acute Exacerbations of COPD
- Algorithm C: Management of COPD in the Hospital or Emergency Department

Scope

Disease/Condition(s)

Chronic obstructive pulmonary disease (COPD)

Other Disease/Condition(s) Addressed

- Alpha-1 antitrypsin (AAT) deficiency
- Anxiety
- Asthma
- Cardiovascular disease
- Sleep disorder
- Tobacco dependence

Guideline Category

Diagnosis

Evaluation

Management

Treatment

Clinical Specialty

Emergency Medicine

Family Practice

Internal Medicine

Nursing

Pulmonary Medicine

Intended Users

Advanced Practice Nurses

Hospitals

Nurses

Pharmacists

Physician Assistants

Physicians

Respiratory Care Practitioners

Guideline Objective(s)

To assist primary care providers in treating and managing patients with chronic obstructive pulmonary disease (COPD)

Target Population

Adults with a diagnosis or a suspicion of chronic obstructive pulmonary disease (COPD)

Note: The patient population of interest is adults (men and women) who are eligible for care in the Veterans Health Administration (VHA) or the Department of Defense (DoD) health care delivery systems. Patients with bronchiectasis, asthma, cystic fibrosis, or other chronic lung diseases but without COPD are not considered in this clinical practice guideline.

Interventions and Practices Considered

Diagnosis/Evaluation

1. Spirometry
2. Classification of chronic obstructive pulmonary disease (COPD) into 2 groups (those with and those without frequent exacerbations)
3. Offering prevention and risk reduction efforts including smoking cessation and vaccination
4. Investigating comorbid diagnoses as indicated
5. Sleep evaluation
6. Testing for alpha-1 antitrypsin (AAT) deficiency
7. Referral to a pulmonologist (patients with AAT deficiency)

Management/Treatment

Management in the Outpatient Setting

1. Pharmacologic therapy
    - Inhaled short-acting beta 2-agonists (SABAs)
    - Use of spacers

- Long-acting bronchodilators
- Inhaled long-acting antimuscarinic agent (LAMA) tiotropium as first-line maintenance therapy
- Short-acting antimuscarinic agents (SAMAs)
- Inhaled long-acting beta 2-agonists (LABAs)
- Inhaled corticosteroids (ICS) (not as first-line monotherapy)
- Combination therapy (LAMAs, LABAs and ICS)
- Roflumilast (not recommended without consultation with pulmonologist)
- Macrolides (not recommended without consultation with pulmonologist)
- Theophylline (not recommended without consultation with pulmonologist)
- Use of cardio-selective beta-blockers
- Cautious use of hypnotics for insomnia
- Consultation with psychiatrist and/or pulmonologist for anxiety treatment

2. Non-pharmacologic therapy as first-line therapy for chronic insomnia
3. Long-term oxygen therapy (LTOT)
4. Referral for pulmonary consultation for stable hypercapnea
5. Supported self-management
6. Use of telehealth for ongoing monitoring and support
7. Pulmonary rehabilitation
8. Breathing exercises
9. Nutrition referral
10. Referral to a pulmonologist for evaluation before lung volume reduction surgery (LVRS) and lung transplant

Management of Acute Exacerbation

1. Antibiotics
    - Doxycycline
    - Trimethoprim/sulfamethoxazole (TMP-SMX)
    - Second-generation cephalosporin
    - Amoxicillin
    - Amoxicillin/clavulanate
    - Azithromycin
    - Broader spectrum antibiotics (e.g., quinolones)
2. Systemic corticosteroids

Management in the Hospital or Emergency Department

1. Airway clearance techniques utilizing positive expiratory pressure (PEP) devices
2. Early use of non-invasive ventilation (NIV)

Note: The following interventions were considered but there was insufficient evidence to recommend:

N-acetylcysteine (NAC)
Procalcitonin-guided antibiotic use

Major Outcomes Considered

- Quality of life (QoL)
- Morbidity
- Dyspnea
- Functional capacity
- Exacerbation rate and/or severity
- Mortality
- Health care utilization
- Diagnostic test accuracy
- Symptom burden
- Disease progression

Methodology

Methods Used to Collect/Select the Evidence

Searches of Electronic Databases

Searches of Unpublished Data

Description of Methods Used to Collect/Select the Evidence

Formulating Evidence Questions

The Clinical Practice Guideline (CPG) Champions were tasked with identifying key evidence questions to guide the systematic review of the literature on chronic obstructive pulmonary disease (COPD). These questions, which were developed in consultation with the Lewin Group's evidence review team, ECRI Institute, addressed clinical topics of the highest priority for the Department of Veterans Affairs (VA) and Department of Defense (DoD) populations. The key questions (KQs) follow the population, intervention, comparison, outcome, timing, and setting (PICOTS) framework for evidence questions, as established by the Agency for Healthcare Research and Quality (AHRQ). Table A-1 in the original guideline document provides a brief overview of the PICOTS typology.

The Champions and evidence review team carried out several iterations of this process, each time narrowing the scope of the CPG and the literature review by prioritizing the topics of interest. Table A-2 in the original guideline document contains the final set of KQs used to guide the systematic review for this CPG.

Conducting the Systematic Review

The methods of the systematic review are described below. In part, these methods followed the guidelines for conducting a systematic review set forth by AHRQ in the *Methods Guide for Effectiveness and Comparative Effectiveness Reviews*. Additionally, the methods followed the guidance set forth by the VA/DoD in the *Guideline for Guidelines* document (see the "Availability of Companion Documents" field).

For all KQs, the following external and internal databases were searched: MEDLINE, PreMEDLINE, EMBASE, (via the OVID SP platform using the one-search and de-duplication features), the Cochrane Database of Systematic Reviews, the Database of Abstracts of Reviews of Effects, and the Health Technology Assessment Database. Searches were designed to identify unique reviews, trials, and technology assessments. Searches of the World Wide Web were also performed to capture relevant grey literature that had not been indexed to the databases listed previously. The searches covered the time period of January 1, 2005 to February 2014. The search strategy was based on a combination of Medical Subject Headings (MeSH) terminology and text key words, and can be found in Table A-3 in the original guideline document. The syntaxes used to search each of the previously listed databases can be found in Tables A-4 and A-5 in the original guideline document.

Extensive literature searches identified 2,717 citations potentially addressing the KQs of interest to this evidence review. In each stage of the evidence review process, studies were included or excluded based on a set of criteria (see table below). Of the original 2,717 identified studies, 1,110 were excluded upon title review for clearly not meeting inclusion criteria (e.g., not pertinent to the topic, not published in English, published prior to study inclusion publication date, or not a full-length article). Overall, 1,607 abstracts were reviewed with 836 of those being excluded for the following reasons: not a systematic review or clinical study, did not address a KQ of interest to this review, did not enroll population of interest, or published prior to January 2005. A total of 771 full-length articles were reviewed. Of those, 317 were excluded at a first pass review for the following: not addressing a KQ of interest, not enrolling the population of interest, not meeting inclusion criteria for clinical study or systematic review, or being a duplicate. A total of 454 full-length articles were thought to address one or more KQs and were further reviewed. Of these, 360 were ultimately excluded. Reasons for their exclusion are presented in Figure A-1 in the original guideline document. Overall, the original searches identified 94 studies that addressed one or more of the KQs and were considered as evidence in this review. Table A-2 in the original guideline indicates the number of studies that addressed each of the questions. Subsequent searches were conducted to identify new studies or studies covering clinical areas not covered in the original systematic review. These searches identified additional studies that were incorporated as evidence in the final CPG.

Table: Criteria for Study Inclusion and Exclusion

General Criteria
• Clinical studies or systematic reviews published on or after January 1, 2005 to February 2014. If multiple systematic reviews addressed

a KQ, the most recent and/or comprehensive review were selected. Systematic reviews will be supplemented with clinical studies published subsequent to the systematic review.
- Studies must be published in English.
- Publication must be a full clinical study or systematic review; abstracts alone were not included. Similarly, letters, editorials, and other publications that were not full-length, clinical studies were not accepted as evidence.
- Study must have enrolled a patient population in which at least 85 percent of patients had COPD, with identifiable data for the population of interest (i.e., patients with COPD should be identifiable in the dataset).
- Only studies assessing the efficacy of drugs that have received United States Food and Drug Administration (FDA) approval for marketing in the US were included in this review.

Screening, Treatment and Management Studies

- For KQ 1, studies focusing on COPD biomarkers were not included as evidence addressing this KQ. Further, studies addressing this KQ must have reported on patient outcomes or on other outcomes of interest to the question, which include improvement in diagnoses or clinical classification, treatment planning, and clinician adherence to treatment protocols.
- For KQ 1, 8, 9, non-randomized controlled trials (RCTs), case-controlled trials, and other observational studies were accepted as evidence. Case studies or narrative reviews were not accepted as evidence for these KQs.
- For KQs 2, 3, 4a, 4b, 5 a-j, 6, and 7, study must have been a systematic review of RCTs or an RCT. Observational studies were not considered as evidence for these questions.
- Study must have enrolled at least 20 patients (10 per study group).
- Study must have reported on an outcome of interest.
- For KQ 4, short-term antibiotic use was defined as 21 days or less.

Number of Source Documents

The original searches identified 94 studies that addressed one or more of the key questions (KQs) and were considered as evidence in this review. See Figure A-1 in the original guideline document for a systematic review flow diagram.

Methods Used to Assess the Quality and Strength of the Evidence

Weighting According to a Rating Scheme (Scheme Given)

Rating Scheme for the Strength of the Evidence

Quality of Evidence and Definitions*

High quality — Further research is very unlikely to change confidence in the estimate of effect.
Moderate quality — Further research is likely to have an important impact on confidence in the estimate of effect and may change the estimate.
Low quality — Further research is very likely to have an important impact on confidence in the estimate of effect and is likely to change the estimate.
Very low quality — Any estimate of effect is very uncertain.

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Methods Used to Analyze the Evidence

Review of Published Meta-Analyses

Systematic Review with Evidence Tables

Description of the Methods Used to Analyze the Evidence

Abstracting and Managing Data

For each study included in this review, the following study level details were abstracted: country, purpose, and quality rating. For previous systematic reviews, reviewers reported the search strategy used, study selection criteria, and overall information about the evidence base, including number of included studies and overall patients enrolled. For all studies, reviewers abstracted data about characteristics of the included patients and interventions being assessed.

Assessing Individual Studies' Methodological Quality (i.e., Internal Validity or Risk of Bias)

As per the Department of Veterans Affairs/Department of Defense (VA/DoD) *Guideline for Guidelines* document (see the "Availability of Companion Documents" field), risk-of-bias (or study quality) of individual studies and previous systematic reviews was assessed using the U.S. Preventive Services Task Force (USPSTF) method. Each study was assigned a rating of "Good," "Fair," or "Poor" based on sets of criteria that vary depending on study design. Detailed lists of criteria and definitions of "Good," "Fair," or "Poor" ratings for different study designs appear in Appendix VII of the USPSTF procedure manual.

Data Synthesis

A narrative approach to synthesizing the evidence for all the key questions (KQs) was used. As indicated in the VA/DoD *Guideline for Guidelines* document, the first-line of evidence was previous systematic reviews. For questions in which a previous review was available, individual studies that met this review's inclusion criteria were used to supplement or update the previous review. For questions for which no previous review was available, reviewers summarized the overall findings for the outcomes of interest of the studies that addressed a KQ.

Assessing the Overall Quality of the Body of Evidence for and Outcome

The overall quality of the body of evidence supporting the findings for the outcomes of interest in this report was assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system. The GRADE system primarily involves consideration of the following factors: overall study quality (or overall risk of bias or study limitations), consistency of evidence, directness of evidence, and precision of evidence. Given time and resources, other factors such as publication bias may also be considered.

The GRADE system rates the overall quality of the evidence as "High," "Moderate," "Low," and "Very Low" (see the "Rating Scheme for the Strength of the Evidence" field). For instance, a body of evidence that consists of randomized controlled trials (RCTs) automatically starts with a rating of high quality. This rating can be downgraded if some of the RCTs have serious flaws such as lack of blinding of outcome assessors, not reporting concealment of allocation, or high dropout rate. Similarly, the quality can be downgraded or further downgraded if inconsistencies of findings are present or if there is a lack of precision surrounding an outcome's effect size. For more information on the GRADE system go to the GRADE working group website at the following link: http://www.gradeworkinggroup.org/.

Assessing Applicability

When describing the evidence base addressing a KQ, the evidence review team discussed aspects of the included studies, such as characteristics of included patients and treatments being assessed that may make the overall findings of the studies more or less applicable to the population, treatments, or outcomes of interest to this review.

Methods Used to Formulate the Recommendations

Expert Consensus

Description of Methods Used to Formulate the Recommendations

The methodology used in developing the 2014 Clinical Practice Guideline (CPG) follows the *Guideline for Guidelines*, an internal document of the Department of Veterans Affairs/Department of Defense (VA/DoD) Evidence-Based Practice Working Group (EBPWG) (see the "Availability of Companion Documents" field). This document provides information regarding the process of developing guidelines, including the identification and assembly of the Guideline Champions (Champions) and other subject matter experts from within the VA and the DoD, known as the Work Group, and ultimately, the submission of an updated chronic obstructive pulmonary disease (COPD) CPG to the EBPWG.

The Champions and Work Group for this CPG were charged with updating the 2007 evidence-based clinical practice recommendations and publishing a guideline document to be used by providers within the VA/DoD health care system. Specifically, the Champions for this guideline were responsible for identifying the key questions (KQs) of greatest clinical relevance, importance, and interest for the management of patients with

COPD. In addition, the Champions assisted in:

1. Conducting the evidence review, including providing direction on inclusion and exclusion criteria
2. Assessing the level and quality of the evidence
3. Identifying appropriate disciplines to be included as part of the Work Group
4. Directing and coordinating the Work Group
5. Participating throughout the guideline development and review processes

The Lewin Team (Team), including DutyFirst Consulting, ECRI Institute, and Sigma Health Consulting, LLC, was contracted by the VA and the DoD to support the development of this CPG and conduct the evidence review. The Team held the first conference call in September 2013, with participation from the contracting officer's representatives (COR), leaders from the VA Office of Quality, Safety and Value and the DoD Office of Evidence Based Practice, and the Champions. During this call, the project team discussed the scope of the guideline initiative, the roles and responsibilities of the Champions, the project timeline, and the approach for developing specific research questions on which to base a systematic review on the diagnosis and management of COPD. The group also identified a list of clinical specialties and areas of expertise that are important and relevant to the management of COPD from which the Work Group members were recruited. The specialties and clinical areas of interest included: family practice, internal medicine, nurse case management, nursing, pharmacy, pulmonology, social work, primary care, physical therapy, nutritional service, and dietetics.

The guideline development process for the 2014 CPG consisted of the following steps:

1. Formulating evidence questions (key questions)
2. Conducting the systematic review
3. Convening a three and one-half day face-to-face meeting with the CPG Champions and Work Group members
4. Drafting and submitting a final CPG on the management of COPD to the VA/DoD EBPWG

The KQs were developed specifically to address the current state of COPD treatment and management and significant scientific developments since the 2007 guideline. The questions selected were of high priority for the VA and the DoD key populations. Each question focused on a specific population, intervention, comparison, and outcome.

These KQs guided a systematic evidence review, which identified the body of evidence relevant to each KQ. The overall quality of the body of evidence was assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology, which takes multiple factors (overall study quality, consistency of evidence, directness of evidence, and precision of evidence) into consideration to rate the overall quality of the evidence as "High," "Moderate," "Low," and "Very Low."

At a three and one-half day face-to-face meeting, the CPG Champions and Work Group members, with support from the Team, drew on the body of evidence to develop recommendations. During this process, they took into account the GRADE rating for the strength of the evidence, as well as a number of other factors (balance of desirable and undesirable outcomes, values and preferences, and other considerations), to rate the strength of the recommendation as "Strong For," "Weak For," "Strong Against," or "Weak Against." They also reconciled the new recommendations with the 2007 CPG recommendations. Following, the face-to-face meeting, the Champions and Work Group members drafted the CPG document. They submitted a final CPG document in December 2014.

Appendix A in the original guideline document provides a more detailed description of each of these tasks.

Reconciling 2007 CPG Recommendations

Evidence-based CPGs should be current, which typically requires revisions based on new evidence or as scheduled subject to time-based expirations. For example, the US Preventive Services Task Force (USPSTF) has a process for refining or otherwise updating its recommendations pertaining to preventive services. Further, the inclusion criteria for the National Guideline Clearinghouse (NGC) specify that a guideline must have been developed, reviewed, or revised with the past five years.

The COPD Guideline Work Group focused largely on developing new and updated recommendations based on the evidence review conducted for the priority areas addressed by the KQs. In addition to those new and updated recommendations, the Guideline Work Group considered the current applicability of other recommendations that were included in the previous CPG on management of COPD, published in 2007, subject to evolving practice in today’s environment. Subject to Guideline Work Group consensus, recommendations that were no longer relevant to the current practice environment, or were otherwise out of scope for this CPG, were not carried forward to this CPG. Recommendations that were considered to be relevant to the current practice environment and still in scope for this CPG, and that required no substantive (i.e., entailing clinically meaningful) rewording, were carried forward in this CPG. The wording was, however, modified slightly to be best utilized in today's clinical environment and to uphold the GRADE recommendation format. For modified recommendations, the Guideline Work Group referred to

the available evidence as summarized in the body of the 2007 CPG, though not to the evidence review that was conducted for the 2007 CPG. The modified recommendations carried forward from the 2007 CPG were not based on an updated systematic review. These "modified" recommendations are noted in the Recommendations.

The Guideline Work Group recognized the need to accommodate the transition in evidence rating systems from the 2007 CPG to the current CPG. In order to report the strength of all recommendations using a consistent format (i.e., the GRADE system), the Guideline Work Group converted the USPSTF strengths of the recommendation accompanying the carryover recommendations from the 2007 guideline to the GRADE system. As such, the Guideline Work Group considered the strength of the evidence cited for each recommendation in the 2007 CPG as well as harms and benefits, values and preferences, and other implications, where applicable. In some instances, evidence published since the 2007 CPG was considered along with the evidence base used for that CPG.

The Guideline Work Group recognizes that, while there are practical reasons for incorporating findings from a previous systematic review or previous recommendations or recent peer-reviewed publications into an updated CPG, doing so does not involve an original, comprehensive systematic review and therefore may introduce bias.

Convening the Face-to-Face Meeting

In consultation with the COR, the Champions, and the Work Group, the Lewin Team convened a three and one-half day face-to-face meeting of the CPG Champions and Work Group members on April 28-May 1, 2014. These experts were gathered to develop and draft clinical recommendations based on the evidence review for an update to the 2007 CPG. Lewin presented detailed information on the process used to grade the evidence. ECRI presented findings from the evidence review for each of the KQs. The presentations helped prepare the Champions and Work Group for their work in reviewing and synthesizing the evidence and forming new recommendations.

Under the direction of the Champions, the Work Group members were charged with interpreting the results of the evidence review and were asked to retain, revise, or reject each recommendation from the 2007 CPG. In addition, members developed new clinical practice recommendations, not presented in the 2007 CPG, based on the 2013 evidence review. At this meeting, Work Group members were assigned to one of four smaller subgroups depending on their area of clinical expertise.

Grading Recommendations

This CPG uses the GRADE methodology to assess the quality of the evidence base and assign a grade for the strength for each recommendation. The GRADE system uses the following four domains to assess the strength of each recommendation:

- Balance of desirable and undesirable outcomes
- Confidence in the quality of the evidence
- Values and preferences
- Other implications, as appropriate, e.g.,:
    - Resource Use
    - Equity
    - Acceptability
    - Feasibility
    - Subgroup considerations

Refer to the original guideline document for further descriptions of each domain.

The framework in Table A-7 in the original guideline document was used by the Work group to guide discussions on each domain.

The strength of a recommendation is defined as the extent to which one can be confident that the desirable effects of an intervention outweigh its undesirable effects and is based on the framework above, which combines the four domains. GRADE methodology does not allow for recommendations to be made based on expert opinion alone. While strong recommendations are usually based on high or moderate confidence in the estimates of effect (quality of the evidence) there may be instances where strong recommendations are warranted even when the quality of evidence is low. In these types of instances where the balance of desirable and undesirable outcomes and values and preferences played large roles in determining the strength of a recommendation, this is explained in the discussion section for the recommendation in the original guideline document.

The GRADE of a recommendation is based on the following elements:

- Four decision domains used to determine the strength and direction (described above)
- Relative strength (Strong or Weak)

- Direction (For or Against)

Drafting and Submitting the Final CPG

Following the face-to-face meeting, the Champions and Work Group members were given writing assignments for the update of specific sections of the 2007 COPD CPG that would form portions of the narrative text for the 2014 COPD CPG. During this time, the Champions also revised the 2007 COPD algorithms and identified the content for the guideline summary and pocket card, as part of the provider toolkits that will be developed by the Office of Evidence-Based Practice, HQ MEDCOM following the publication of the 2014 COPD CPG. The algorithms are included as part of this COPD CPG to provide a clear description of the flow of patient care. The final 2014 COPD CPG was submitted to the EBPWG in December 2014.

Rating Scheme for the Strength of the Recommendations

The relative strength of the recommendation is based on a binary scale, "Strong" or "Weak." A strong recommendation indicates that the Work Group is highly confident that desirable outcomes outweigh undesirable outcomes. If the Work Group is less confident of the balance between desirable and undesirable outcomes, they present a weak recommendation.

Similarly, a recommendation for a therapy or preventive measure indicates that the desirable consequences outweigh the undesirable consequences. A recommendation against a therapy or preventive measure indicates that the undesirable consequences outweigh the desirable consequences.

Using these elements, the grade of each recommendation is presented as part of a continuum:

- Strong For (or "The Expert Panel recommends offering this option …")
- Weak For (or "The Expert Panel suggests offering this option …")
- Weak Against (or "The Expert Panel suggests not offering this option …")
- Strong Against (or "The Expert Panel recommends against offering this option …")

Note that weak (For or Against) recommendations may also be termed "Conditional," "Discretionary," or "Qualified." Recommendations may be conditional based upon patient values and preferences, the resources available, or the setting in which the intervention will be implemented. Recommendations may be at the discretion of the patient and clinician or they may be qualified with an explanation about the issues that would lead decisions to vary.

Cost Analysis

A formal cost analysis was not performed and published cost analyses were not reviewed.

Method of Guideline Validation

External Peer Review

Internal Peer Review

Description of Method of Guideline Validation

A thorough explanation of the guideline validation process and public comment is provided in the Department of Veterans Affairs and the Department of Defense (VA/DoD) *Guideline for Guidelines* document (see the "Availability of Companion Documents" field).

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

The type of evidence supporting the recommendations is not specifically stated.

Table A-2 in the original guideline documents indicates the number and type of studies that addressed each of the questions. The evidence base consists primarily of systematic reviews and randomized controlled trials.

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

- Formulation of an efficient and effective assessment of the patient's condition
- Optimizing the use of therapy to reduce symptoms and enhance functionality
- Minimizing preventable complications and morbidity
- Emphasizing the use of personalized, proactive, patient-driven care

Potential Harms

- Theophylline has associated harms. Because it is metabolized through the cytochrome P450 pathway, there may be significant associated food and medication interactions. Patients receiving theophylline had significantly greater risk of experiencing nausea compared to patients receiving placebo. It is also associated with adverse reactions including insomnia, anxiety, nausea, vomiting, tremor, arrhythmias, delirium, seizures, and death.
- In pooled study results, adverse events were more common in patients receiving roflumilast compared to placebo. Gastrointestinal events such as diarrhea, nausea, vomiting, dyspepsia, and abdominal pain were observed more frequently in patients treated with roflumilast than placebo. There was also a higher risk of psychiatric adverse events in patients receiving roflumilast 500 mcg compared to placebo. Adverse events reported include insomnia or sleep disorders, anxiety, and depression. Suicidal ideation and behavior, including completed suicide, were reported in clinical trials. Patients with psychological disorders were generally excluded in the clinical trials. Therefore, it is unknown what risk roflumilast poses in populations such as those served by the Department of Veterans Affairs/Department of Defense (VA/DoD), where the risk for psychiatric disorders may be more common.
- Observational studies have not shown an increase in mortality using cardio-selective beta-blockers in patients with chronic obstructive pulmonary disease (COPD). Due to the limited data on the subject, beta-blockers should be used with caution, and patients should be monitored for an increase in COPD symptoms.
- Modest harms associated with home non-invasive ventilation (NIV) include upper airway irritation, highly variable patient acceptability, and significant resource implications.
- See Table D-2 in the original guideline document for information on adverse effects of specific pharmacological interventions.

Contraindications

Contraindications

- Long-acting beta 2-agonists (LABAs) increase the risk of asthma-related death and should not be used as monotherapy in patients with asthma.
- Each drug class has agents available in a dry powder formulation. Dry powder formulations contain lactose and small amounts of milk proteins and should not be used in patients with severe hypersensitivity to milk proteins.

Qualifying Statements

Qualifying Statements

- The Department of Veterans Affairs (VA) and the Department of Defense (DoD) guidelines are based upon the best information available at the time of publication. They are designed to provide information and assist decision-making. They are not intended to define a standard of

care and should not be construed as one. Neither should they be interpreted as prescribing an exclusive course of management.

- This Clinical Practice Guideline (CPG) is based on a systematic review of both clinical and epidemiological evidence. Developed by a panel of multidisciplinary experts, it provides a clear explanation of the logical relationships between various care options and health outcomes while rating both the quality of the evidence and the strength of the recommendations.
- Variations in practice will inevitably and appropriately occur when clinicians take into account the needs of individual patients, available resources, and limitations unique to an institution or type of practice. Every healthcare professional making use of these guidelines is responsible for evaluating the appropriateness of applying them in the setting of any particular clinical situation.
- These guidelines are not intended to represent TRICARE policy. Further, inclusion of recommendations for specific testing and/or therapeutic interventions within these guidelines does not guarantee coverage of civilian sector care. Additional information on current TRICARE benefits may be found at www.tricare.mil or by contacting your regional TRICARE Managed Care Support Contractor.

Implementation of the Guideline

Description of Implementation Strategy

The chronic obstructive pulmonary disease (COPD) Clinical Practice Guideline (CPG) and algorithms are designed to be adapted by individual facilities in consideration of local needs and resources. The algorithm serves as a guide that providers can use to advise their patients on best interventions and timing of care in order to optimize quality of care and clinical outcomes.

Although this CPG represents medical practice on the date of its publication, the practice is evolving. This evolution requires continuous updating based on published research. New technology and additional research may improve patient care in the future. The CPG can assist in identifying priority areas for research and optimal allocation of resources. Future studies examining the results of CPG implementation may lead to the development of new practice-based evidence.

Implementation Tools

Clinical Algorithm

Patient Resources

Pocket Guide/Reference Cards

Quick Reference Guides/Physician Guides

Resources

For information about availability, see the *Availability of Companion Documents* and *Patient Resources* fields below.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Getting Better

Living with Illness

IOM Domain

Effectiveness

Identifying Information and Availability

Bibliographic Source(s)

Management of Chronic Obstructive Pulmonary Disease Working Group. VA/DoD clinical practice guideline for the management of chronic obstructive pulmonary disease. Washington (DC): Department of Veterans Affairs, Department of Defense; 2014 Dec. 94 p. [216 references]

Adaptation

Not applicable: The guideline was not adapted from another source.

Date Released

1999 Aug (revised 2014 Dec)

Guideline Developer(s)

Department of Defense - Federal Government Agency [U.S.]

Department of Veterans Affairs - Federal Government Agency [U.S.]

Veterans Health Administration - Federal Government Agency [U.S.]

Source(s) of Funding

United States Government

Guideline Committee

Management of Chronic Obstructive Pulmonary Disease Guideline Working Group

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Financial Disclosures/Conflicts of Interest

A hallmark of the Department of Veterans Affairs and the Department of Defense (VA/DoD) guidelines is their relative freedom from conflict of interest. Conflicts of interest faced by the VA/DoD Evidence-Based Practice Working Group (EBPWG) and the working groups that it charters to develop specific guidelines are handled based on the Veterans Health Administration (VHA) Handbook 1004.07 - Financial Relationships between VHA Health Care Professionals and Industry, which was signed October 21, 2009. All EBPWG meetings utilize the process of real-time verbal disclosure as required by VHA Handbook 1004.07 - Information for Members of VHA Decision Making and Advisory Groups.

At the start of this guideline development process and at other key points throughout, the project team was required to submit disclosure statements to reveal any areas of potential conflict of interest in the past two years, including verbal affirmations of no conflict of interest at regular meetings. The project team was also subject to random web-based surveillance (e.g., ProPublica). If there was a positive (yes) conflict of interest response (actual or potential), then action was taken by the co-chairs and evidence-based practice program office, based on level and extent of involvement to mitigate the conflict of interest. Actions ranged from restricting participation and/or voting on sections related to a conflict, to removal from the Work Group. Recusal was determined by the individual, co-chairs, and evidence-based practice office. No member of the final project team had any conflict of interest.

Guideline Status

This is the current release of the guideline.

This guideline updates a previous version: Management of COPD Working Group. VA/DoD clinical practice guideline for the management of outpatient chronic obstructive pulmonary disease. Washington (DC): Department of Veterans Affairs, Department of Defense; 2007. 138 p.

This guideline meets NGC's 2013 (revised) inclusion criteria.

Guideline Availability

Electronic copies: Available from the Department of Veterans Affairs Web site .

Print copies: Available from the Department of Veterans Affairs, Veterans Health Administration, Office of Quality and Performance (10Q) 810 Vermont Ave. NW, Washington, DC 20420.

Availability of Companion Documents

The following are available:

- VA/DoD clinical practice guideline for the management of chronic obstructive pulmonary disease. Clinician summary. Washington (DC): Department of Veterans Affairs, Department of Defense; 2014 Dec. 16 p. Electronic copies: Available from the Department of Veterans Affairs (VA) Web site .
- VA/DoD clinical practice guideline for the management of chronic obstructive pulmonary disease. Pocket card. Washington (DC): Department of Veterans Affairs, Department of Defense; 2014 Dec. 6 p. Electronic copies: Available from the VA Web site .
- Guideline for guidelines. Washington (DC): Department of Veterans Affairs; 2013 Apr 10. Electronic copies: Available from the VA Web site .
- Putting clinical practice guidelines to work in VHA. Washington (DC): Department of Veterans Affairs. 64 p. Electronic copies: Available from the VA Web site .

In addition, a pharmacotherapy table is available in Appendix D of the original guideline document .

Print copies: Department of Veterans Affairs, Veterans Health Administration, Office of Quality and Performance (10Q) 810 Vermont Ave. NW, Washington, DC 20420.

Patient Resources

The following is available:

- VA/DoD clinical practice guideline for the management of chronic obstructive pulmonary disease. Patient summary. Washington (DC): Department of Veterans Affairs, Department of Defense; 2014 Dec. 6 p. Electronic copies: Available from the Department of Veterans Affairs Web site .

Please note: This patient information is intended to provide health professionals with information to share with their patients to help them better understand their health and their diagnosed disorders. By providing access to this patient information, it is not the intention of NGC to provide specific medical advice for particular patients. Rather we urge patients and their representatives to review this material and then to consult with a licensed health professional for evaluation of treatment options suitable for them as well as for diagnosis and answers to their personal medical questions. This patient information has been derived and prepared from a guideline for health care professionals included on NGC by the authors or publishers of that original guideline. The patient information is not reviewed by NGC to establish whether or not it accurately reflects the original guideline's content.

NGC Status

This NGC summary was completed by ECRI on September 9, 1999. The information was verified by the guideline developer on January 10, 2000. The summary was updated by ECRI on May 6, 2001. This summary was updated by ECRI Institute on October 28, 2008. This summary was updated by ECRI Institute on January 30, 2015. This summary was updated by ECRI Institute on May 18, 2016 following the U.S. Food and Drug Administration advisory on Fluoroquinolone Antibacterial Drugs.

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